

3 WHAT IS CLAIMED IS:

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5 1. A method of modulating the expression of a nucleic
6 acid in the hepatic system of a mammal, comprising
7 the step of:

8 administering to said mammal an oligonucleotide
9 which hybridizes to said nucleic acid to modulate
10 the expression of said nucleic acid,

11 wherein said oligonucleotide has at least two
12 sterol moieties covalently bonded thereto.

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14 2. The method of claim 1, wherein said oligonucleotide
15 is an antisense nucleotide.

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17 3. The method of claim 1, wherein at least one of said
18 sterol moieties is a cholesteryl moiety.

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20 4. The method of claim 1, wherein said oligonucleotide
21 comprises two cholesteryl moieties.

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23 5. The method of claim 1, wherein said sterol moieties
24 are bound at the 2'-O, 3'-O or 5'-O positions of
25 said oligonucleotide.

26

27 6. A method of preferentially targeting an antisense
28 oligonucleotide to liver cells in a mammal,
29 comprising the steps of:

30 covalently bonding said oligonucleotide to at
31 least two sterol moieties to form a sterol-
32 oligonucleotide conjugate; and

1 administering said sterol-oligonucleotide
2 conjugate to said mammal to preferentially target
3 said oligonucleotide to said liver cells in said
4 mammal to modulate the expression of a gene in said
5 liver cells.

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7 7. The method of claim 6, wherein said liver cells are
8 endothelial cells.

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10 8. The method of claim 6, wherein said oligonucleotide
11 is an antisense nucleotide.

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13 9. The method of claim 6, wherein at least one of said
14 sterol moieties is a cholestryl moiety.

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16 10. The method of claim 6, wherein said oligonucleotide
17 comprises two cholestryl moieties.

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19 11. The method of claim 6, wherein said sterol moieties
20 are bound at the 2'-O, 3'-O or 5'-O positions of
21 said oligonucleotide.

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23 12. A method of treating an animal having a hepatic
24 disease or disorder associated with a protein
25 encoded by a gene, comprising the step of:

26 administering to said mammal an oligonucleotide
27 which hybridizes to said gene,

28 wherein said oligonucleotide has at least two
29 sterol moieties covalently bonded thereto.

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31 13. The method of claim 12, wherein said oligonucleotide
32 is an antisense nucleotide.

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- 1 14. The method of claim 12, wherein at least one of said
2 sterol moieties is a cholesteryl moiety.
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- 4 15. The method of claim 12, wherein said oligonucleotide
5 comprises two cholesteryl moieties.
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- 7 16. The method of claim 12, wherein said sterol moieties
8 are bound at the 2'-O, 3'-O or 5'-O positions of
9 said oligonucleotide.
10
- 11 17. A composition, comprising an oligonucleotide,
12 wherein said oligonucleotide has at least two
13 sterol moieties covalently bonded thereto.
14
- 15 18. A composition, wherein said oligonucleotide is an
16 antisense nucleotide.
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- 18 19. The composition of claim 17, wherein at least one of
19 said sterol moieties is a cholesteryl moiety.
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- 21 20. The composition of claim 17, wherein said
22 oligonucleotide comprises two cholesteryl moieties.
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- 24 21. The composition of claim 17, wherein said sterol
25 moieties are bound at the 2'-O, 3'-O or 5'-O
26 positions of said oligonucleotide.
27
- 28 22. The composition of claim 17, wherein said
29 oligonucleotide hybridizes to a gene encoding a
30 protein that is overexpressed or abnormally
31 expressed in hepatic tissues in the course of a
32 disease or a disorder.